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Review article

Intracranial bleedings in patients on long-term anticoagulant treatment: Benefits from oral thrombin and factor Xa inhibitors in clinical practice

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ABSTRACT

Dabigatran, a direct thrombin inhibitor and activated factor X inhibitors, rivaroxaban and apixaban, used in the prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation (AF), have several advantages over vitamin K antagonists (VKAs). The non-vitamin K oral anticoagulants (NOACs) have been shown to reduce the risk of intracranial bleedings by 50%. The current review summarizes the available data on the epidemiology, mechanisms and treatment of intracranial bleedings observed on oral anticoagulation with the focus on the specificity of NOACs in this context.

1. Introduction

Atrial fibrillation (AF) is the most common preventable cause of ischaemic stroke in the general population, with an increasing prevalence with age from 1% to above 20% at the age of 80–89 [1]. Strokes associated with AF, which represent 15–20% of all strokes, have a high mortality up to 20–25% within the first 30 days, since the ischaemic event commonly causes severe neurological deficits [1]. The incidence of AF-associated stroke decreases by 65% with oral vitamin K antagonist (VKA) therapy. However, almost 50% of AF patients do not receive anticoagulation [2,3]. Although effective, the major obstacle to the use of VKAs is bleeding complications. Intracranial bleeding is the most devastating complication of VKA use, comprising about 8.7% of all major bleeding episodes and resulting in a 46–55% mortality rate [4].

The anticoagulants, previously termed new oral anticoagulants, comprise a thrombin inhibitor, dabigatran, and two activated factor X (FXa) inhibitors, rivaroxaban and apixaban, which are approved worldwide for the prevention of stroke and peripheral embolism in patients with nonvalvular AF [5].

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Table 1 – Characteristics of target-specific oral anticoagulants (reprinted from Undas A et al. [6] with permission of the publisher Medycyna Praktyczna).

Variable	Warfarin	Dabigatran etexilate[a]	Rivaroxaban	Apixaban
Mode of action	↓ Synthesis vitamin K-dependent coagulation factors	Direct selective and reversible thrombin inhibitor	Direct selective and reversible activated factor X inhibitor	Direct selective and reversible activated factor X inhibitor
Time to peak plasma concentration	90 min (peak action after 4–5 d)	0.5–2 h	2–4 h	1–4 h
Half-life	36–42 h	12–14 h	5–9 h (young) 11–13 h (age >65 y)	8–13 h
Substrate of P-glycoprotein transporter	No	Yes	Yes	Yes
Substrate of CYP enzymes	Yes (CYP3A4, CYP2C9)	No	Yes (CYP3A4/5, CYP2J2)	Yes (CYP3A4, CYP2C9)
Route of elimination	Various[c]	80% renal	66% renal (33% unchanged)	25% renal
Protein binding	99%	35%	90%	90%
Basic daily dose in AF	~5 mg (1–18 mg) Target INR, 2–3	2 × 150 mg	1 × 20 mg	2 × 5 mg
Reduced daily dose	Not applicable	2 × 110 mg[b]	1 × 15 mg	2 × 2.5 mg
Indications for reduced dosage	Not applicable	– CrCl, 30–49 ml/min – HAS-BLED ≥3 points – Age ≥80 y – Coadministration of verapamil	– CrCl, 30–49 ml/min – HAS-BLED ≥3 points	– Creatinine ≥133 μM – Age ≥80 y – Body weight ≤60 kg (2 or 3 criteria met)

[a] A prodrug that undergoes biotransformation to the active molecule, dabigatran, by esterases.
[b] In the United States: 2 × 75 mg daily (2 × 110 mg not approved).
[c] The anticoagulant effect of warfarin is eliminated through synthesis of functionally active coagulation factors rather than through elimination of warfarin; coagulation factor synthesis is hastened by exogenous vitamin K.
Abbreviations: INR, international normalized ratio.

Compared with VKAs, the non-vitamin K oral anticoagulants (NOACs) are characterized by rapid onset of action, shorter half-life, few drug–drug interactions, a predictable anticoagulant response, and no need for routine coagulation monitoring (Table 1) [6].

The benefits of NOACs in nonvalvular AF have been documented in large clinical trials (Randomized Evaluation of Long-Term Anticoagulation Therapy [RELY], Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation [ROCKET-AF], Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation [ARISTOTLE]) [7,8]. The use of all the three NOACs was non-inferior to therapy with VKAs in reducing stroke or systemic embolism in patients with nonvalvular AF. The current European Society of Cardiology (ESC) Guidelines on the Management of AF recommend long-term anticoagulation in all patients with nonvalvular AF with at least moderate (1 point in the CHA_2DS_2-VASc score) thromboembolic risk [9]. Of note, NOACs are a preferred prophylactic option over VKAs in nonvalvular AF patients [10]. Indirect analysis including 14,527 patients treated with NOACs showed that these anticoagulants were associated with reduced risk of stroke or systemic embolism (odds ratio [OR], 0.85; 95% CI, 0.74–0.99) compared with warfarin [11].

2. Characteristics of intracranial bleeding in patients anticoagulated with NOACs

Large randomized controlled trials [7–9], nationwide cohort studies in real-world general practice settings in American [12], Asian [13] and European [14] populations have compellingly shown that the use of NOACs in patients with AF results in markedly fewer intracranial haemorrhagic adverse events (0.3–0.6 per 100 patient-years) as compared to warfarin. The reduced risk of intracranial bleeding is one of the major advantages of these agents over VKAs. There are no direct head-to-head comparisons of NOACs in this regard. Effectiveness and safety of all the NOACs approved to clinical use are supported by several meta-analyses [15–19]. Trials on NOACs in AF patients have demonstrated that the lowest rate of intracranial haemorrhage (ICH) as compared to warfarin was observed for dabigatran at a dose of 110 mg BID, while the highest rate of ICH and the highest hazard ratio (HR) were observed for rivaroxaban (Table 2) [7–9]. During dabigatran treatment with a dose of 150 mg BID intracerebral and subdural haemorrhages were the most common types of ICH (46% each), but the rate of subdural haematoma did not differ from that observed in patients treated with warfarin [the rate per 100 patient-years was 0.20 vs. 0.31, respectively; HR (95% CI): 0.65 (0.39–1.1), $P < 0.01$]. Dabigatran at a dose of 110 mg BID significantly reduced the risk of all types of ICH including traumatic ICH as compared to warfarin [20]. Moreover, the incidence of ICH in subjects treated with apixaban at a daily dose of 5 mg (2.5 mg BID) is comparable with that observed in patients treated with aspirin 81–324 mg daily, so in terms of ICH apixaban seems to be the safest of all NOACs [21,22]. The absolute rates of fatal intracranial haemorrhages were lower with dabigatran than with warfarin [20]. However, there were no differences in fatal ICH between the treatment with rivaroxaban and warfarin [23]. Such detailed subanalysis was not performed in trials with apixaban where the rate of fatal ICH was calculated together with other

Table 2 – The rate of intracranial haemorrhages on NOACs.

Drug	Dose	Rate of intracranial haemorrhage (%/year) Studied drug vs. warfarin	Hazard ratio[a] (95% CI)	Rate of haemorrhagic stroke (%/year) Studied drug vs. warfarin	Hazard ratio[a] (95% CI)
Dabigatran etexilate	2 × 110 mg	0.23 vs. 0.76	0.30 (0.19–0.45); $P < 0.001$	0.12 vs. 0.38	0.31 (0.17–0.56); $P < 0.001$
	2 × 150 mg	0.31 vs. 0.76	0.40 (0.27–0.59); $P < 0.001$	0.10 vs. 0.38	0.26 (0.14–0.49); $P < 0.001$
Rivaroxaban	1 × 20 mg	0.5 vs. 0.7	0.67 (0.47–0.93); $P = 0.02$	No data	No data
Apixaban	2 × 5 mg or 2 × 2.5 mg	0.33 vs. 0.80	0.42 (0.30–0.58); $P < 0.001$	0.24 vs. 0.47	0.51 (0.35–0.75); $P < 0.001$

[a] Hazard ratios are for the NOAC group as compared to the warfarin group.

bleeding events [15]. A recent systematic review and meta-analysis to examine the impact of bleeding complications of NOACs compared with the VKAs in patients with venous thromboembolism or AF has demonstrated that ICH occurred in 297 of 57,850 (0.51%) patients treated with NOACs and in 485 of 44,757 (1.08%) patients treated with VKAs in the 12 studies reporting this outcome. NOACs were associated with a significant reduction in intracranial bleeding (RR 0.43 [95% CI, 0.37–0.50], $P < 0.01$, $I^2 = 2\%$). The pooled absolute risk reduction was −0.57%, resulting in an NNT of 185. Analysis with a fixed-effects model did not change the results [24].

Direct, well-designed randomized controlled trials would be needed to specify clinically relevant differences between individual NOACs. The frequency of intracranial bleeding as a complication of treatment with NOACs does not depend on the previous stroke. Such therapy seems to be safe in both primary and secondary stroke prevention in patients with AF, although there are only limited data about NOACs for secondary stroke prevention, since patients in the subacute phase of stroke and with severe stroke within the past 6 months were excluded from the RE-LY and ROCKET-AF trials [7–9].

Current recommendations discourage the addition of aspirin to anticoagulation therapy in most patients with cardioembolic stroke since there is clear evidence that combined therapy in AF increases the risk of all bleeding events [25–28]. The exception to this may represent the patients with clinically evident coronary artery disease (CAD), particularly an acute coronary syndrome or those following implantation of drug-eluting stents. In this group the NOACs might become an important alternative to VKAs. In the trials RE-LY, ROCKET-AF and ARISTOTLE 30–40% of patients in the compared treatment groups were taking aspirin, usually at a daily dose of less than 100 mg. In the post hoc analysis of the RE-LY trial, concomitant aspirin use was the key modifiable independent risk factor for ICH but only in patients treated with warfarin and not in those treated with dabigatran [20]. Further sub-analysis based on the results of the RE-LY trial confirmed that there were fewer ICH on both doses of dabigatran than on warfarin, regardless of antiplatelet treatment. However, one should keep in mind that concomitant treatment with antiplatelet agent(s) leads to a significant rise in the overall risk of major bleeding when combined with any oral anticoagulant [28]. Such analyses on other NOACs are not available until now, and dedicated trials are required since no comparison of combined therapy with antiplatelet drug and warfarin (or NOACs) to warfarin/NOACs alone has been done so far, specifically in stroke populations.

There is a paucity of data available to clinically characterize ICH that occurs on NOACs.

The effect of NOACs on the volume of extravasated blood and outcome is currently being investigated. An experimental model of NOAC-associated intracerebral haemorrhage has been recently developed [29,30]. Unexpectedly, after induction of intracerebral bleeding by collagenase injection or laser beam, the volume of extravasated blood did not increase in dabigatran or rivaroxaban treated mice compared with non-coagulated controls. Despite haemostasis and prolonged bleeding time being affected, the therapy had no effect on functional outcome. Increased volume of extravasated blood and worse functional outcome were triggered only by very high doses of the drug resulting in elevated dabigatran plasma concentrations of up to almost ten times therapeutic values observed in humans.

Recently the first attempts were made to summarize clinical characteristics of ICH during NOAC treatment. An analysis of 17 patients who experienced ICH while treated with dabigatran has been published [31]. In 8 patients stable volume of extravasated blood as the outcome was reported, but in 3 patients the expansion of ICH resulted in death. In another study 5 patients with ICH on rivaroxaban have been compared to those treated with warfarin. As might be expected from experimental studies, a significantly smaller size of extravasated blood was found in subjects on NOACs. Moreover, even though the patients were at high risk of bleeding (HAS-BLED score of 3), ICH expansion was not observed in any patient treated with rivaroxaban, while it occurred in 20% of patients on warfarin [32]. It may be a result of a favourable limiting influence of rivaroxaban on the haematoma enlargement. Unfortunately, the small number of patients on NOACs is likely to make the analysis underpowered, the results cited above are preliminary, and the issue requires further investigation.

3. Potential mechanisms of beneficial effects of NOACs on intracranial bleeding

The pathomechanism of anticoagulant-associated ICH is not fully recognized. The major background is impaired haemostasis, but it is unknown whether anticoagulants affect the integrity of the cerebral vessels. The pathophysiology of differences between ICH on NOACs vs. warfarin remains unclear. The presumed mechanism results from the special local haemostatic conditions within the brain vasculature. The subendothelial layer of cerebral vessels contains high

concentrations of tissue factor (TF). Any endothelial injury and bleeding outside the vessel wall and then into brain parenchyma result in excessive binding of TF to circulating activated factor VII (VIIa). It initiates the intrinsic coagulation pathway by activation of factors IX and X, leading then to the prothrombinase complex formation [33]. Selective inhibitors of activated factor X (rivaroxaban, apixaban) and of thrombin (dabigatran) do not affect the interaction between TF and factor VIIa, whereas warfarin does so, suppressing the hepatic production of factor VII. Warfarin that inhibits vitamin K-dependent gamma-carboxylation of the coagulation factors II, VII, IX and X reduces their activity in plasma. Thereby it effects both the initiation and amplification of thrombin generation unpredictably. Therefore the quantity of thrombin that the coagulation system generates in response to the injury of the vascular wall is lower during treatment with warfarin than NOACs, since the latter target only one element of the coagulation cascade (factor Xa or thrombin) in a stoichiometric ratio of 1:1 [34]. It might allow for feedback mechanisms within the coagulation pathway to prevent enlargement of haematoma. However, the theory based on the role of TF may be questioned, since the NOACs reduce the rates of both intracerebral and subdural haematomas, whereas the pathophysiology of the latter is different and the role of TF is not so prominent. One wonders why treatment with another direct thrombin inhibitor, lepirudin, resulted in haematoma enlargement in experimental studies. Possible advantages of dabigatran over lepirudin are the result of the selective binding of dabigatran only to the active site of the thrombin molecule while two exosites are available for other blood coagulation proteins. This monovalent binding of dabigatran with thrombin influences only reversible thrombin inhibition. In the situation of excessive thrombin generation for example following the vascular wall injury, thrombin inhibition can be overcome [35].

An interesting observation from experimental studies is that rivaroxaban and apixaban exert a protective effect on the neurovascular unit (NVU) after thrombolysis. The interactions between compounds of NVU as pericytes and astrocytes through neurotrophins correlate with neuron survival under hypoxia. Ischaemic injury of pericytes disturbs reflow within the microcirculation and limits delivery of substrates, and the narrow gap between pericytes and astrocytes is crucial in this exchange. Unlike the pre-treatment with NOACs, in warfarin pre-treated rats a marked dissociation between the astrocyte foot process and pericytes under recombinant tissue plasminogen activator (r-tPA) treatment was observed. NOACs dramatically reduce such a complication. This observation might provide additional explanation for the advantages of NOACs over warfarin in both ischaemic and haemorrhagic cerebral lesions [36].

4. Patients at elevated risk of intracranial bleeding

According to the results of the large trials on NOACs and warfarin as a comparator, independent predictors of developing anticoagulant-associated ICH during treatment with novel anticoagulants were: Asian or Black race, increasing age, uncontrolled hypertension, especially increased diastolic blood pressure, previous stroke or transient ischaemic attack (TIA), concomitant use of antiplatelet drugs and reduced platelet count below 210×10^9/L. The specific condition that increases the risk of intracerebral bleeding during antithrombotic treatment is cerebral amyloid angiopathy (CAA) representing deposition of β-amyloid within the wall of the cerebral small vessels. Even beside the antithrombotic treatment, CAA results in symptomatic intracerebral haemorrhage and asymptomatic cerebral microbleeds (CMBs). The CMBs correspond to the deposits of hemosiderin located around sclerotic vessels, and their prevalence increases with age. They are associated with lesions below 10 mm in diameter detected with special sequences of magnetic resonance imaging (MRI) as T2 gradient-recall echo (GRE) and susceptibility-weighted imaging (SWI) sequences. There are two typical locations of CMBs, deep subcortical and infratentorial, which correspond to vascular disease, in particular hypertension, and lobar disease, associated with apolipoprotein E (ApoE) ε2/ε4 genotype carrier and CAA confirmed in an autopsy. Patients with ischaemic stroke or TIA and with CMBs are as much as three times more likely to have either haemorrhagic transformation of ischaemic lesions or recurrent haemorrhagic stroke [37–40]. The risk of fatal intracerebral haemorrhage increases with the number of CMBs. Two-year risk of intracerebral bleeding is calculated as 8% if more than 5 CMBs are present. In a meta-analysis of antithrombotic treatment, CMBs were more common in patients on warfarin or antiplatelet agents and with intracerebral haemorrhage than in those with ischaemic stroke or TIA. Thus in patients with multiple CMBs the risk of fatal ICH may even outweigh the benefits of antithrombotic therapy [41,42]. The risk of ICH in patients treated with NOAC and burdened with CMBs remains to be clarified. The novel antithrombotic therapy may be beneficial in this group of patients, but there are insufficient data to mandate changes in the previously chosen drug regimen only because of CMBs. The irreversibility of the NOACs and lack of antidotes in setting of a putative ICH supports such a cautious approach.

The risk of ICH might be stratified according to the useful $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scales. The risk of ICH on dabigatran increased with higher $CHADS_2$ scores, while in patients on apixaban the rate of ICH was lower in patients with high $CHADS_2$ scores compared to those with lower scores, and relative ICH risk reduction tended to be greater in patients with HAS-BLED scores of 3 or more as compared to warfarin [43].

5. Treatment of ICH on NOACs

There is no specific antidote available for any of the NOACs, and clinical experience with haemostatic agents in NOAC-associated bleeding is scarce. Therefore, nonspecific reversal therapies may be considered based on available, but limited, evidence [44,45]. Use of either agent is based on poor-quality data and as such should not be considered a requirement in the setting of intracranial bleeding. The therapeutic options presented below are based on the experts' opinion, while the manufacturers' recommendations from the product characteristics are very limited and mainly apply the overdosage of NOACs.

5.1. *Dabigatran*

Soon after ingestion, the absorption of lipophilic dabigatran may be reduced by gastric lavage and/or administration of charcoal. Activated prothrombin complex concentrate (aPCC) (80 U/kg) is slightly preferred over 3-factor (FII, IX, X) prothrombin complex concentrate (PCC), or 4-factor (FII, VII, IX, X) PCC, because it may improve hemostasis, probably by providing small amounts of thrombin. Alternative agents, such as recombinant activated factor VII (rVIIa), have not been demonstrated to reverse bleeding on dabogatran. Dabigatran, which is in only 35% bound to plasma proteins, can be removed by hemodialysis; 49–68% of active dabigatran can be removed after 4 h of hemodialysis in patients with end-stage renal disease. Duration of dialysis appears to have the greatest impact on dabigatran plasma concentrations [46]. In a recent case series, plasma dabigatran levels were reduced by 52–77% in 5 dabigatran-treated patients with life-threatening bleeding following treatment with hemodialysis. Three of the 5 patients experienced rebound increases in dabigatran concentration following hemodialysis, likely related to drug redistribution from the extravascular compartment [45].

5.2. *Rivaroxaban and apixaban*

Because of a high degree of albumin binding in plasma, rivaroxaban and apixaban are not dialyzable. Charcoal hemoperfusion removes highly protein bound drugs, but, to our knowledge, there are no studies assessing the removal of rivaroxaban or apixaban with hemodialysis or charcoal hemoperfusion. All measurable anticoagulant effects of these drugs are reversed by 4-factor PCC, as studied in healthy volunteers [47]. Clinical data are still lacking, but it seems reasonable to administer a dose of 50 IU/kg or a standard dose of 2000 IU in case of ICH. It is unknown whether this needs to be repeated and whether 3-factor PCC is effective for reversal of rivaroxaban.

5.3. *Adjunctive hemostatic therapies*

There have been no studies evaluating the efficacy and safety of desmopressin (1-desamino-8-D-arginine vasopressin) in the context of NOAC-associated bleeding. Because desmopressin promotes release of von Willebrand factor from endothelial cells, it is biologically plausible (although unproven) that desmopressin could be of benefit to a patient with NOAC-associated bleeding. If repeated doses are given, close monitoring of serum electrolytes is required due to the potential for hyponatremia.

Tranexamic acid stabilizes fibrin clots by interfering with fibrinolysis and can also be used as adjunctive therapy for severe bleeding in a variety of circumstances. Its hemostatic efficacy in the setting of NOAC-associated bleeding is unknown.

5.4. *Specific antidotes*

Several antidotes for the NOACs are in clinical development. Andexanet alfa (a recombinant FXa derivative lacking catalytic and membrane-binding activity) is a modified factor Xa molecule used to directly reverse effects of apixaban, rivaroxaban, and edoxaban. It binds the anticoagulant drug, thus making the patient's own factor Xa molecule available to participate in blood coagulation. A phase III study (ANNEXA-R) testing the safety and efficacy of the antidote recently reached its primary end point. In this trial, an 800-mg intravenous bolus of andexanet alfa, which was tested in 41 healthy volunteers treated with rivaroxaban 20 mg for 4 days and then subsequently randomized to the study drug or placebo, ''immediately and significantly'' reversed the steady-state anticoagulation activity of rivaroxaban. Idarucizumab (aDabi-Fab) is a humanized mouse monoclonal antibody fragment directed against dabigatran. A phase III study of patients on dabigatran with major bleeding or needing emergency surgery is under way. Aripazine is a small synthetic molecule (a D-arginine compound) that appears to have broad activity against dabigatran, rivaroxaban, apixaban, edoxaban, and heparins. A first study investigating the drug's effect on edoxaban-treated human volunteers has been completed [48].

6. The use of antithrombotic therapy in patients with a prior ICH

The use of antithrombotic therapies to prevent thromboembolism in patients with an acute or prior ICH presents a clinical dilemma with competing risks and benefits. In many cases, clinical decisions must be made on the basis of indirect and observational evidence rather than high quality clinical trials. In the absence of randomized controlled trials to address these treatment dilemmas, the European Stroke Organization did not make firm recommendations about whether and when to resume antithrombotic drugs after intracranial haemorrhage [44]. Suggested timings for restarting these drugs range from not earlier than 14 days up to 10 to 30 weeks. Left atrial appendage occlusion could be an alternative for managing patients in AF with a high risk of cardioembolic stroke after acute ICH [49].

It is important to prevent deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in patients with ICH. In immobile patients with ICH intermittent pneumatic compression (IPC) has been shown to improve outcome and reduce the risk of DVT. In the CLOTS-3 trial comparing IPC vs. no IPC for immobile patients with stroke, IPC was superior for the prevention of the primary outcome of proximal DVT within 30 days (8.5% vs. 12.1%; OR 0.65, 95% CI 0.51–0.84; $P = 0.001$), patients with ICH seemed to benefit at least as much as patients with ischaemic stroke (OR 0.36, 95% CI 0.17–0.75 vs. OR 0.72, 95% CI 0.55–0.93; $P = 0.057$), and IPC may be superior for the prevention of death within six months (adjusted HR 0.86, 95% CI 0.74–0.99; $P = 0.042$) [50]. There is insufficient evidence from randomized controlled trials to make strong recommendations about how, when, and for whom anticoagulation should be given to prevent DVT or improve outcome [44]. The latest Antithrombotic Therapy and Prevention of Thrombosis American College of Chest Physicians Evidence-Based Clinical Practice Guidelines and Polish Guidelines of Prophylaxis and Treatment of Venous Thromboembolism published in 2012 suggested that if thrombotic risk persists, pharmacologic thromboprophylaxis using subcutaneous low-molecular-

weight heparin in a low dose once daily may be substituted for mechanical thromboprophylaxis in patients with ICH, starting on day 2–4 after bleeding, if there are no signs of haematoma expansion [51,52].

7. Laboratory monitoring during therapy with NOACs

It is well known that the use of NOACs eliminates the need for routine laboratory monitoring. A major clinical situation in which laboratory monitoring of NOACs could be considered is life-threatening bleeding, in particular ICH. Other potential indications to determine blood concentrations of NOACs include: the exclusion of persistent anticoagulant effects before surgery or an invasive procedure when the patient has taken the drug in the previous 24 h, or longer if creatinine clearance is reduced; identification of sub-or supra-therapeutic levels in patients taking other drugs that are known to significantly affect pharmacokinetics or those at extremes of body weight; reversal of anticoagulation; suspicion of overdose; and finally, assessment of compliance in patients suffering thrombotic events whilst on treatment [6,53,54].

A method for the precise measurement of circulating levels of NOACs used in several trials is liquid chromatography–tandem mass spectrometry (LC–MS/MS). In clinical practice the dilute thrombin time (TT) for dabigatran or anti-Xa activity for rivaroxaban or apixaban, using the appropriate calibrators (not those used to monitor low-molecular-weight heparins), is used. These coagulometric tests provide results that well correlate with the values obtained using LC–MS/MS [55,56]. It has already been recommended using the TT-based assay to rather accurately estimate concentrations of dabigatran >50 ng/ml [55].

NOACs may alter routine coagulation tests within the first hours following drug intake in most subjects. Within the first 2–8 h after intake of dabigatran, depending on renal function and the analyzer and reagent used to perform the test, the activated partial thromboplastin time (aPTT) may be prolonged to between 40 and 60 s, with a linear relationship with dabigatran concentrations up to 200 ng/ml. In patients treated with dabigatran, TT is prolonged at low concentrations and exceeds the upper limit of the reference range as plasma levels rise. A normal TT excludes significant plasma concentrations of dabigatran, which is in stark contrast to rivaroxaban and apixaban, which do not prolong the TT. In patients receiving rivaroxaban, prothrombin time (PT) values are often elevated above the upper limit of the reference range, leading to an increased international normalized ratio (INR) calculated by most automatic analyzers. Of note, results of routine laboratory tests determined after administration of NOACs display substantial differences that largely depend on the thromboplastin or PT reagents used to perform the tests. Routine coagulation tests cannot be used to monitor NOACs. In addition, NOACs may interfere with other clot-based tests such as clotting factor levels, antithrombin (false normal results in deficient patients on dabigatran in a thrombin-based assay), protein C (false normal results in deficient patients on dabigatran), lupus anticoagulant (false positive results in some patients at peak plasma concentrations of drug and a majority of patients on rivaroxaban with no consistent effect of apixaban), thrombin generation, thromboelastography and others [53–56]. Importantly, the effects of NOACs on antithrombin, protein C and protein S assays were dependent on the type of reagent. Measurements of plasma D-dimer concentrations are unaffected by NOACs.

The first Polish experience with the use of the HEMOCLOT assay to measure dabigatran concentrations that has been approved for clinical use in Europe, as well as that of calibrated chromogenic factor Xa assays, has been recently published [57,58].

To interpret the results of the tests, the exact time of the blood sample acquisition relative to the intake of the last dose of NOACs is of key importance. Renal function assessment is also helpful [48]. Until now, ''cut-off points'' between which anticoagulation with NOACs is therapeutic (the equivalent of the therapeutic range known for VKA) have not been defined [59]. In the case of ICH or other severe bleeding, plasma levels of dabigatran and rivaroxaban above 50 ng/ml strongly suggest detectable anticoagulant effects, which indicates that the complication is likely associated with the agents. This result could be useful when it is unclear when the patients with ICH have taken the last dose of NOACs.

Ischaemic stroke treated with thrombolysis is another specific clinical situation when knowledge on the coagulation status and plasma concentration of NOAC is required. Thrombolytic treatment is allowed in subjects anticoagulated with vitamin K antagonists when INR is below 1.7 [60]. However, in patients treated with NOACs no decision-making model has been developed, and reports on such treatment are limited to case studies. Recently Kate et al. proposed a thrombolysis protocol for acute ischaemic stroke in patients taking dabigatran. The authors presumed conservative but arbitrary thresholds for dabigatran plasma concentrations (below 10 ng/ml), TT (<38 s) and aPTT (<37 s) as the inclusion criteria [61]. However, some investigators reported that the decision-making process should not b based on routine coagulation markers in stroke patients. Folyovich et al. reported a case of doubling of both TT and aPTT within 5 days after stroke in patients pretreated with dabigatran and without any change in anticoagulant treatment after an ischaemic event [62]. Since the number of patients anticoagulated with NOACs continues to grow, there is a need to develop a specific approach in this clinical setting.

Taken together, laboratory monitoring of NOACs should be implemented in reference centres taking care of patients with stroke as well as those with ICH.

8. Conclusions

In conclusion, the rate of ICH in patients with AF treated with NOACs is significantly lower as compared to warfarin. Experimental and clinical studies suggest that NOACs might have a less detrimental effect on ICH outcome than warfarin. Intracranial haemorrhage on NOACs seems to be characterized by lower volume and smaller expansion. The strongest risk factors for ICH to be considered before a decision on the management are as follows: older age, greater number of CMBs in MRI, presence of ApoE ε2/ε4 genotype and concomitant

treatment with antiplatelet drugs. Increasing use of NOACs worldwide is likely to lower the incidence of the most dangerous complication of long-term anticoagulation and thus improving the safety of ischaemic stroke prevention administered in the right patients at the right time.

Conflict of interest

A.U. has received honoraria from Boehringer Ingelheim, Bayer Healthcare, Glaxo-Myers-Squibb, Sanofi-Aventis and Pfizer. K. Z. has received honoraria from Bayer Healthcare and Pfizer. M. L. declares no conflict of interest.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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